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OIAC Ontario Immunization Advisory Committee
CCOI Comité consultatif ontarien de l'immunisation

Recommendations: Measles Post-Exposure Prophylaxis for Individuals Who Are Immunocompromised Due to Disease or Therapy

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Overview

The increase in measles activity observed in Ontario starting in 2024 highlighted the need for more detailed guidance on measles post-exposure prophylaxis (PEP) for individuals with weakened or impaired immune systems due to disease or therapies (herein referred to as 'immunocompromised') than what was currently available in provincial and national guidelines.[1,2] To address this gap, the topic was brought to the Ontario Immunization Advisory Committee (OIAC) with the goal of developing measles PEP guidance for high-risk populations. Target audiences for this guidance include public health staff responsible for managing contacts of confirmed measles cases, as well as clinicians providing care to patients who are immunocompromised who may be consulted to determine the appropriate post-exposure management strategy.

The scope of the guidance was limited to defining 'immunocompromised' as it relates to identifying appropriate measles PEP strategies (e.g., immunoglobulin [Ig] products versus measles, mumps and rubella [MMR] vaccine) and the potential use of serology to inform management of contacts who are immunocompromised. Details regarding other aspects of measles PEP (e.g., guidance on intramuscular [IMIg] or intravenous Ig [IVIg] product use), contact management and other public health interventions (e.g., exclusion) were considered out of scope. These topics are detailed in other guidance, which should be used in combination with OIAC recommendations to best inform the management of individuals exposed to measles.[1]

Three OIAC meetings (March 27, April 10 and June 12, 2024) were held to review relevant scientific literature and a jurisdictional scan of measles PEP guidance. Feasibility considerations on proposed PEP strategies were also examined, which was facilitated by presentations and input from representatives from the Ontario Regional Blood Coordinating Network and Public Health Ontario's (PHO) laboratory, which serves as the provincial reference lab for public health microbiology testing, including measles. Given the limited published data, consultation with external experts was also integrated in the OIAC guidance development process. Specialists in the fields of infectious diseases, immunology/allergy, gastroenterology, hematology, transplant and human immunodeficiency virus (HIV) care reviewed the draft guidance and provided insights to ensure that recommendations were aligned with best clinical practice and evidence. As the National Advisory Committee on Immunization (NACI) was also in the process of reviewing measles PEP guidance, the OIAC collaborated with the NACI secretariat to promote consistency between provincial and national guidance. Following the consultation process, invited external experts were given an opportunity to review the revised guidance through an electronic survey in September 2024. Recommendations were voted on and approved by the OIAC in October 2024.

The approach undertaken by the OIAC facilitated the development of measles PEP recommendations for individuals who are immunocompromised that provide clear and comprehensive guidance and acknowledge the heterogeneity in immunocompromising conditions and therapies.

Summary of Recommendations: The OIAC developed comprehensive guidance on measles PEP for individuals who are immunocompromised based on scientific and feasibility considerations and guided by clinical input from external experts.

The recommendations for individuals with an absence or a near-absence of a functioning immune system (Group A), individuals who may be able to maintain adequate immunity from past infection or vaccination (Group B), and individuals with only low-level immunosuppression or only mild immunocompromising conditions (Group C) may be found in Table 1.

Background

Contacts of measles cases must promptly be identified and assessed for susceptibility to infection. Several factors, including year of birth, vaccination status, laboratory-confirmed measles infection history, pre-existing medical conditions, and if available, measles IgG serology, can inform the need for measles PEP.[1] In Ontario, administration of MMR vaccine within 72 hours of exposure is recommended for susceptible immunocompetent contacts aged ≥6 months with no contraindications to vaccination; however, MMR is contraindicated for individuals with certain immunocompromising conditions or receiving certain therapies, and other individuals who are immunocompromised may not be able to mount an adequate response to vaccination.[1,3] Ig prophylaxis is used for susceptible contacts at higher risk of disease severity (e.g., immunocompromised, pregnant individuals, and infants), and may be administered intramuscularly (IMIg) or intravenously (IVIg) within 6 days of exposure.[1]

Certain immunocompromising conditions and therapies make it unlikely that a person will develop or maintain immunity against measles despite a history of infection or vaccination.[1] Additionally, individuals who are immunocompromised, especially those with severely impaired cell-mediated immunity, are at high risk of developing severe disease and/or complications from measles, including pneumonitis, encephalitis, and death.[1,4,5] For these susceptible individuals, the timely administration of measles PEP can mitigate the risk of infection and/or reduce the clinical severity of disease.[6–11]

Ontario saw increased measles activity in 2024 and continuing into 2025, with a higher than expected number of confirmed and probable cases compared with previous years.[12] In March 2024, Ontario released the updated Infectious Disease Protocol Appendix 1: Case Definitions and Disease-Specific Information for measles.[1] The document outlines guidance on measles PEP strategies for susceptible individuals, including individuals aged ≥6 months who are immunocompromised, based on the 2018 guidance from NACI.[2] The updated measles Appendix 1 did not provide a comprehensive definition of immunocompromising conditions, but referred to the Canadian Immunization Guide (CIG) and guidance from the United Kingdom Health Security Agency (UKHSA) for additional details and considerations.[3,13]

The CIG indicates that a dose of Ig should be considered for: 1) HIV-infected individuals with severe immunosuppression even with documented previous MMR immunization, and 2) hematopoietic stem cell transplant (HSCT) recipients regardless of pre-transplant vaccination status, unless vaccinated post-HSCT with adequate measles antibody titres.[3] However, the CIG does not provide a comprehensive list of immunocompromising conditions and therapies, and recommends clinical consultation to evaluate the susceptibility of other individuals who are immunocompromised.

In the absence of detailed national and provincial guidance, uncertainty remained regarding the operationalization of measles post-exposure management of individuals who are immunocompromised. This prompted several requests for consultation with PHO on the topic, with questions often centred on the complexity of identifying the appropriate PEP strategy given the wide spectrum and severity of immunocompromising conditions and therapies.

To address this gap, the topic of measles PEP for individuals who are immunocompromised was brought to the OIAC with the aim of developing more comprehensive guidance for high-risk populations. Considerations included the degree and heterogeneity of immunocompromising conditions, feasibility and logistical considerations, and the potential role of serology in PEP decision-making.

Methods

A targeted evidence review focusing on measles PEP, feasibility and test characteristics of measles IgG serology, impact of immunocompromising conditions and therapies on vaccine response, as well as a jurisdictional scan of measles PEP guidance, was conducted. Three OIAC meetings (March 27, April 10, and June 12, 2024) were held to discuss scientific evidence as well as feasibility and clinical considerations pertaining to measles PEP for individuals who are immunocompromised. Two representatives from the Ontario Regional Blood Coordinating Network were invited to present at the March meeting to provide information on access to Ig products in Ontario and were also in attendance at the April meeting. A representative from PHO's laboratory was also in attendance to answer questions regarding measles IgG serology testing.

In the setting of limited published evidence on the effectiveness of PEP in populations with immunocompromising conditions,[9,11] clinical experts outside of OIAC were consulted to incorporate a broad range of sub-specialized expertise into the guidance development process (see Acknowledgements). Sixteen individuals were identified through recommendations from OIAC members and PHO who represented specialties in adult and pediatric infectious diseases, HIV, transplant, allergy and immunology, gastroenterology, and hematology. Consulted experts received a reviewer package containing background information and draft recommendations and were requested to provide clinical insights and feedback. Five consulted experts were also in attendance during the June meeting to participate in discussions regarding the recommendations.

In February 2025, NACI released updated guidance on measles PEP, including for individuals who are immunocompromised.[14] The OIAC collaborated with the NACI secretariat supporting the measles working group in an effort to ensure consistent guidance to PHUs and health care providers. The OIAC secretariat also presented the draft guidance and external expert feedback to the NACI measles working group in September 2024 and requested input from working group members on the proposed recommendations.

Following the consultation process, the invited external experts were asked to review the revised recommendations through an electronic survey that was launched on August 7, 2024, and closed on September 2, 2024. The finalized recommendations were subsequently voted on electronically and approved by OIAC members on October 22, 2024.

Recommendations

The framework of the OIAC consultation process (Table 1) was drawn from measles PEP guidance from Quebec and the United Kingdom, which categorized immunocompromising conditions and therapies into three distinct categories:

A. Individuals with an absence or a near-absence of a functioning immune system
B. Individuals who may be able to maintain adequate immunity from past infection or vaccination
C. Individuals with only low-level immunosuppression or only mild immunocompromising conditions

Categories were subsequently populated and refined based on the evidence summary and consultation process with external experts. These recommendations are not intended to be prescriptive and should be used to guide clinical decisions.

Table 1: OIAC Recommendations on Measles Post-Exposure Prophylaxis for Individuals Who Are Immunocompromised Due to Disease or Therapy

Group	Definition	Measles Susceptibility Assessment	Time Since Exposure: ≤72 Hours (≤3 Days)	Time Since Exposure: 73 Hours – 6 Days
Group A: Individuals with an absence or near-absence of a functioning immune system	**1. Transplant**[a] • Within 12 months of receiving autologous hematopoietic stem cell transplant (HSCT) or 24 months of receiving allogeneic HSCT or those with chronic graft-versus-host disease • Within 12 months of a solid organ transplant **2. Chimeric antigen receptor (CAR) T-cell therapy** • Within 12 months of undergoing CAR T-cell therapy for malignancy **3. Acute lymphoblastic leukemia**[a] • Acute lymphoblastic leukemia within and until 3 months after completion of chemotherapy or 12 months after completion of B cell depleting therapy **4. Human immunodeficiency virus (HIV) infection**[b] • HIV infection with a current CD4 T cell count <15% (age 1 – 13 years) or <200 cells/mm^3 (age ≥14 years), or a CD4:CD8 ratio <0.5 (adults) **5. Primary immunodeficiency** • Significant primary immunodeficiency or inborn error of immunity (e.g., X-linked agammaglobulinemia, severe combined immunodeficiency, severe antibody deficiency, ataxia-telangiectasia, select defects in intrinsic and innate immunity, etc.) for which live viral vaccines are contraindicated[c,d] **6. Therapies/medications** • Receiving cyclophosphamide or anti-thymocyte globulin • Receiving or completed alemtuzumab or B cell depleting (e.g., rituximab) treatment within the past 12 months[a]	Assume individual is susceptible regardless of year of birth, prior lab-confirmed measles infection, or measles vaccination status	IMIg (bodyweight <30kg) or IVIg (bodyweight ≥30 kg) MMR vaccine is contraindicated	IMIg (bodyweight <30kg) or IVIg (bodyweight ≥30 kg) MMR vaccine is contraindicated

Group	Definition	Measles Susceptibility Assessment	Time Since Exposure: ≤72 Hours (≤3 Days)	Time Since Exposure: 73 Hours – 6 Days
Group B: Individuals who may be able to maintain adequate immunity from past infection or vaccination	**1. Transplant**[a] • >12 months but <24 months post autologous HSCT • >12 months post solid organ transplant **2. CAR T-cell therapy** • >12 months post CAR T-cell therapy[e] **3. Malignancy** • Lymphoproliferative diseases including hematologic cancers (e.g., indolent lymphoma, leukemia or plasma cell lymphoma) except for acute lymphoblastic leukemia • Immunotherapy/targeted cancer therapy/chemotherapy/radiotherapy for malignancy other than acute lymphoblastic leukemia (e.g., solid tumour or hematologic including multiple myeloma) that is ongoing or completed within the last 3 months **4. Secondary immunodeficiency** • Secondary (non-congenital) hypogammaglobulinemia due to disease (e.g., nephrotic syndrome) or therapy (e.g., chemotherapy)[c] **5. Therapies/medications** • Targeted immunosuppressive therapies not mentioned above including cytokine inhibitors (e.g., tumor necrosis factor, IL-1, IL-12/23, IL-17, IL-23), costimulation modulators, and small molecule inhibitors (e.g., JAK inhibitors), alone or in combination with steroids or other immunosuppressive drugs, that are ongoing or received <6 months prior to exposure[f] • Ongoing, <4 weeks since completion, or tapering following daily corticosteroid therapy at a prednisone or equivalent dose of ≥20 mg/day for ≥14 days for adults. High-dose prednisone thresholds for children vary across guidelines and range from ≥0.5 mg/kg/day to ≥2 mg/kg/day.[g] • Ongoing or within 3 months of completing treatment with immunosuppressive drugs for immune-mediated diseases (e.g., methotrexate >0.4 mg/kg/week [children: >10 mg/m^2/week; adults: >15 mg/m^2/week], azathioprine >3 mg/kg/day, 6-mercaptopurine >1.5 mg/kg/day, cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, and small molecule inhibitors)[f]	An individual's susceptibility and need for Ig PEP should be examined regardless of their year of birth, prior lab-confirmed measles infection, or measles vaccination status. • If available, consider rapid measles IgG serology testing if not performed recently.[h] IVIg/IMIg for measles PEP is not recommended for those with a positive measles IgG result after becoming immunocompromised.[i] • If serology is negative or timely measles IgG serology testing is not available (i.e., would not permit administration of Ig within the 6-day window), evaluate the risks versus benefits of PEP, ideally with input from the specialist responsible for the clinical care of the individual or in consultation with an infectious disease expert/immunologist. Risk-benefit assessment should also consider the duration and intensity of measles exposure (e.g., household contact).	IMIg (bodyweight <30kg) or IVIg (bodyweight ≥30 kg) MMR vaccine is not recommended[j]	IMIg (bodyweight <30kg) or IVIg (bodyweight ≥30 kg) MMR vaccine is not recommended[j]

Group	Definition	Measles Susceptibility Assessment	Time Since Exposure: ≤72 Hours (≤3 Days)	Time Since Exposure: 73 Hours – 6 Days
Group C: Susceptible individuals with only low-level immunosuppression or only mild immunocompromising conditions[k]	**1. Transplant** • >24 months following HSCT with no chronic graft-versus-host disease **2. HIV infection[b]** • Asymptomatic HIV-infected patients with CD4 T cell counts ≥15% (age 1 – 13 years) or ≥200 cells/mm^3 (age ≥14 years) with a CD4:CD8 ratio ≥0.5 (adults) **3. Primary immunodeficiencies** • Minor B cell deficiency with intact T cell function not requiring Ig therapy, partial T cell defects, and other primary immune deficiencies or inborn error of immunity for which live viral vaccines are not contraindicated[d] **4. Therapies/medications** • Prednisone or equivalent doses <20 mg/day for adults taken for ≥14 days or receiving alternate day corticosteroid therapy. For children, prednisone thresholds vary from <0.5 mg/kg/day to <2 mg/kg/day across different guidelines[g] • ≥4 weeks after discontinuation of long-term (≥14 days) high-dose systemic steroids, or immediately after discontinuation of high-dose steroids taken for <14 days[g] • Therapies that target immune system components, but are unlikely to impair immune pathways involved in infection prevention or control (e.g., anti-IgE, cytokine inhibitors used in the treatment of atopic dermatitis/asthma) • Methotrexate ≤0.4 mg/kg/week (children: ≤10 mg/m^2/week; adults: ≤15 mg/m^2/week) • Azathioprine ≤3 mg/kg/day[l] • 6-mercaptopurine ≤1.5 mg/kg/day • Hydroxychloroquine (any dose)	For HSCT recipients, assume individual is susceptible unless vaccinated post HSCT and have adequate measles antibody titres. For all other groups except HSCT recipients, assume individual is immune if born before 1970—measles PEP is not recommended for individuals with mildly immunocompromising conditions who are in this age group. Measles PEP should be offered to susceptible individuals born in or after 1970 without at least one of the following [m,n,o]: • Documented evidence of vaccination with 2 valid doses of measles-containing vaccine • Positive measles IgG serology[h] • Documented evidence of past lab-confirmed measles infection	MMR vaccine	MMR vaccine is not intended to provide protection as PEP, but should be offered to provide long-term protection[p]

Notes: CAR, chimeric antigen receptor; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; IgE, immunoglobulin E; IgG, immunoglobulin G; IL-1, interleukin; IL-12, interleukin 12; IL-17, interleukin 17; IL-23, interleukin 23; IMIg, intramuscular immunoglobulin; IVIg, intravenous immunoglobulin; JAK, Janus kinase; MMR, measles, mumps and rubella; PEP, post-exposure prophylaxis.

[a] Immune reconstitution is progressive and may occur sooner than the timeframe indicated. Consultation with the specialist responsible for the clinical care of the individual is recommended.

[b] Individuals with uncontrolled HIV viral loads may be at increased risk of measles complications and may not maintain an adequate immune response to the MMR vaccine. Consultation with the specialist responsible for the clinical care of the individual is recommended.

[c] It takes approximately 3–4 months for IgG levels to reach a steady state in individuals receiving regular immunoglobulin replacement. Individuals with severe primary immunodeficiency or secondary hypogammaglobulinemia on regular immunoglobulin replacement therapy for >4 months do not require additional IVIg for PEP. Consult the specialist responsible for the clinical care of the individual or an infectious disease expert/immunologist if exposure occurs <4 months since the initiation of immunoglobulin replacement therapy. NACI and CDC offer guidance for individuals on Ig replacement therapy.[3,15]

[d] As per the Canadian Immunization Guide, the MMR vaccine is contraindicated in individuals with: major B cell deficiency, severe combined B and T cell immunodeficiency, severe T cell deficiency, leukocyte adhesion defects, Chediak-Higashi syndrome and other defects in cytotoxic granule release, undefined phagocyte defect, defects in alpha or gamma interferon production, and nuclear factor kappa B defects. In addition, MMR vaccine is not recommended for individuals receiving regular Ig replacement therapy.[16]

[e] The timeframe for immune reconstitution following CAR T-cell therapy is variable. Consultation with the specialist responsible for the clinical care of the individual is recommended.

[f] Interval from treatment completion may vary with the type and intensity of treatment. Period may be shortened for biologics/treatments with a shorter duration of effect.

[g] For children, a prednisone dose of 20 mg/day is often equivalent to doses below 2 mg/kg/day. There is no consensus regarding the lowest prednisone or equivalent dose that would be considered immunosuppressive in children; thresholds vary across various guidelines from ≥0.5 mg/kg/day to ≥2 mg/kg/day.[16-18]

[h] To inform PEP decisions, measles IgG serology should either: 1) be done following measles exposure through rapid testing, or 2) have been done prior to measles exposure, but AFTER the individual became immunocompromised. Clinical judgement should be used to determine the suitability of past measles IgG serology, if available.

[i] Results of measles immunity serology from Public Health Ontario are reported as reactive (positive), indeterminate, or non-reactive (negative).

[j] The MMR vaccine may be given in some circumstances in consultation with an infectious disease expert/immunologist. The MMR vaccine is not intended to provide protection as PEP if given >3 days post-exposure; if given >3 days post-exposure, its role is to provide long-term protection.

[k] This guidance document does not provide a comprehensive list of mild immunocompromising medical conditions or therapies that result in low-level immunosuppression. Medications that induce low-level immunosuppression may result in a greater degree of immunosuppression when combined. Assessment of severity of immunocompromising condition is often best determined by consulting with the treating physician, infectious disease, expert/immunologist, or special immunization clinic.

[l] Individuals on azathioprine exhibiting signs of myelosuppression/myelotoxicity should be assessed for susceptibility and need for Ig PEP. Please refer to guidance for ‘Individuals who may be able to maintain adequate immunity from past infection or vaccination‘.

[m] Individuals born before 1970 are generally considered to have presumptive immunity with some exceptions (i.e., healthcare workers).[1,3]

[n] Individuals with unknown measles immunization status should be considered susceptible unless they meet at least one of the other two immune criteria (i.e., measles IgG positive or documented past lab-confirmed measles infection).

[o] In Canada, adults born before 1970 are generally presumed to have acquired immunity through past infection due to high levels of measles circulation up until the 1960s. With the exception of the United States where a birth year threshold of 1957 is used, other countries have had endemic measles circulation until 1970 or later. For this reason, the 1970 birth year threshold can also be applied to individuals born and raised outside of Canada, with the exception of the United States.

[p] Individuals with low-level immunosuppression are managed similarly to immunocompetent contacts who are not recommended to receive Ig as measles post-exposure prophylaxis unless they are under the age of 12 months or susceptible pregnant individuals.

Evidence Summary and Considerations

The following sections will discuss key considerations that shaped the development of OIAC recommendations. Topics that will be covered include:

- Jurisdictional scan of measles PEP guidance for individuals who are immunocompromised
- Measles IgG serology considerations in Ontario
- Risk/benefit assessment
- Clinical considerations for individuals who are immunocompromised

Jurisdictional Scan: Measles PEP Guidance for Populations with Immunocompromising Conditions

The OIAC secretariat performed a jurisdictional scan to examine measles PEP guidance for individuals who are immunocompromised from other countries, as well as NACI and other Canadian provinces and territories, with a specific focus on Quebec guidance that was published in February 2024.[1,2,19,20] The international scan included recommendations from the UKHSA in the United Kingdom, the Communicable Diseases Network Australia (CDNA), as well as the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (Red Book) in the United States.[13,15,21,22] A summary of key similarities and differences between jurisdictional guidance is outlined in Table 2.

Across all jurisdictions examined, Ig PEP is indicated within 6 days of measles exposure; however, there are variations in Ig product preference and criteria for IMIg versus IVIg use (e.g., age versus weight limits). Measles IgG serology is recommended to inform PEP strategies in the United Kingdom, United States, Australia, and Quebec, particularly for individuals with immunocompromising conditions or receiving immunosuppressive therapies who may be able to develop or maintain immunity from past infection or vaccination (e.g., individuals with hematologic malignancies or those on biologic therapies). While there are notable differences in the classification of immunocompromising conditions, all jurisdictions consider HSCT recipients within 12 months of transplant and individuals with severe primary immunodeficiency as highly immunocompromised and recommend the use of Ig PEP upon measles exposure regardless of prior evidence of immunity or vaccination status.

Table 2: Jurisdictional Scan on Measles PEP Guidance for Individuals Who Are Immunocompromised

Country	**Canada** Ontario Measles Appendix 1 (2024)/ NACI (2018)[1,2]	**Canada** Protocole d'immunisation du Québec (2024)[19,20]	**United States** ACIP (2013)[15]	**United States** Red Book (2021)[21]	**Australia** CDNA (2019)[22]	**United Kingdom** UKHSA (2024)[13]
PEP Strategy	Age <6 mo (<30 kg): IMIg Age ≥6 mo: IMIg if <30 kg; IVIg if ≥30 kg	<30 kg: IMIg ≥30 kg: IVIg	Age <12 mo: IMIg Age ≥12 mo: IVIg	Age <12 mo: IMIg Age ≥12 mo: IVIg	IMIg	IVIg
Comprehensive Definition of Immunocompromising Conditions	No	Yes	Yes	Yes	No	Yes
Measles IgG Serology Recommended	No	No, for those with absence or near absence of a functioning immune system Yes, for those with significant immunosuppression	No, for those severely immunocompromised	No, for those severely immunocompromised Yes, for those with low-level immunosuppression	Yes, when possible, for individuals who may maintain immunity	Yes, except for those who are severely immunocompromised or with previous evidence of positive measles IgG serology

Notes: ACIP, Advisory Committee on Immunization Practices; IgG, immunoglobulin G; IMIg, intramuscular immunoglobulin; IVIg, intravenous immunoglobulin; mo, months; NACI, National Advisory Committee on Immunization; PEP, post-exposure prophylaxis.

Measles IgG Serology

Protective immunity to measles is accomplished primarily through humoral immunity, particularly through the presence of high-avidity neutralizing antibodies (Ab) specific for measles virus surface glycoproteins.[23] Serum IgG reactivity is used as a correlate of protection for measles as there is currently no other quantitative measure that more accurately predicts measles immunity. It has been suggested that plaque reduction neutralization test (PRNT) titres ≥200 mIU/mL are protective against infection among immunocompetent individuals, and titres between 120 – 200 mIU/mL protect against clinical signs of disease, but not infection.[24] However, several studies have demonstrated that these correlates of protection are not absolute, with measles infection or mild symptoms developing in individuals with high anti-measles IgG titres.[23,25–28]

While PRNT is considered the gold standard for measuring measles IgG titres, the method is labour-intensive, has a long turn-around time, and is not easily standardized across laboratories.[29] As a result, most laboratories outside of the research setting use more cost-effective, high-throughput enzyme immunoassays. PHO uses the BioPlex2200 platform (Bio-Rad Laboratories, Hercules, California, United States) to perform measles IgG serology testing, which reports results as 'non-reactive', 'indeterminate', or 'reactive' according to an antibody index (AI), and not a titre value. The threshold for 'reactive' equates to a PRNT titre of approximately >192 mIU/mL.[30]

The OIAC recommends that measles IgG serology be considered to inform PEP strategies for individuals who are immunocompromised who may be able to develop or maintain immunity from past vaccination or infection (Group B). The detection of a reactive measles IgG titre in these individuals would indicate that the administration of IVIg/IMIg would not have substantial benefit for them, thereby minimizing both the potential harm to the individual of receiving a blood product and the costs to the health system of obtaining, distributing, and administering Ig. However, there are several feasibility, logistical and clinical factors to consider, including those outlined below:

- **Feasibility:** PHO provides measles IgG serology services in Ontario, with tests currently being performed at the Toronto, Kingston and London locations. Routine turnaround time for measles IgG serology is approximately 5 days from receipt of the specimen; however, urgent testing is available with a 2- to 3-hour turnaround time from specimen receipt provided advanced notification to Customer Service (416-235-6556 or 1-877-604-4567) and communication with the laboratory occurs. Several factors may affect turnaround time of measles IgG serology including: timing of specimen acquisition (e.g., after hours, weekends), specimens failing to meet criteria for acceptance, transport logistics, and geographic location.
- **Timeliness**: While Ig PEP may be administered up to 6 days post exposure, prompt administration is recommended as its effectiveness is expected to decrease with increasing time from exposure. Timing of when contacts are identified, as well as logistical considerations affecting the turnaround time for measles IgG serology results and/or the ability to obtain and administer Ig products in a timely manner, may also impact the feasibility of measles IgG serology to aid in PEP decision-making.
- **Waning measles immunity**: Studies have demonstrated waning measles immunity following the onset of certain immunocompromising medical conditions and treatment, which has implications for the timing of the measles IgG serology result in relation to the onset of disease or treatment and its value in informing PEP decisions for individuals who are immunocompromised. For example, waning of immunity has been noted with HSCT recipients, with severity and kinetics associated with the type of conditioning regimen used, time since transplant, presence of graft-versus-host disease and source of immunity (i.e., infection versus vaccination).[31–33] Loss of measles immunity has also been described among children with acute lymphoblastic leukemia and other malignancies as well as solid

organ transplant recipients.[34–45] These studies, along with expert opinion from clinicians consulted by the OIAC, all indicate that decisions regarding the need for Ig PEP following measles exposure for individuals who are immunocompromised should be based on current or recent serology, rather than historic results (i.e., prior to becoming immunocompromised). Clinical judgement should be used to determine the suitability of past measles IgG serology, if available.

Risk Assessment

These OIAC recommendations are not intended to be prescriptive and should only be used as a guide. Public health staff and health care providers responsible for the management of measles contacts who are immunocompromised must always consider both the potential risks and benefits of PEP and the values and preferences of individuals. Assessment of the degree of immunocompromise and what PEP management strategy is most appropriate using the framework outlined by OIAC is best determined through consultations with the treating physician, immunologists, infectious disease specialists or experts from specialty vaccination clinics. For some patient populations, timely measles IgG serology may also play a role in guiding PEP decisions.

In addition to the degree and nature of the immunocompromising condition or treatment, the risk-benefit assessment should consider the intensity and duration of contact with the case(s) of measles. For example, intense and prolonged contact to measles for a household measles contact is associated with a different degree and probability of exposure than someone who learns via a public news release they may have been exposed to measles at a community exposure location.[46–49]

Clinical Considerations for Populations with Immunocompromising Conditions

The OIAC recommendations on measles PEP for populations with immunocompromising conditions are generally aligned with the CIG chapter on immunization of populations who are immunocompromised and the widely accepted classification of immunocompromising conditions developed by the Infectious Diseases Society of America (IDSA) with a few key exceptions (Table 1).[16,17] The rationale behind these divergences are outlined below.

Glucocorticoids

IDSA guidelines indicate that prednisone doses >2 mg/kg/day taken for ≥14 days for individuals <10 kg are highly immunosuppressive.[17] However, pediatric specialists consulted by OIAC noted that doses of prednisone or prednisolone (dose equivalent glucocorticoids) that are well below the IDSA threshold are considered highly immunosuppressive in children. Guidance from the European Alliance of Association for Rheumatology (EULAR) sets the pediatric high-dose threshold at ≥0.5 mg/kg/day of prednisolone, and notes that chronically administered glucocorticoid dose of 20 mg/day is equivalent to dosages below 2 mg/kg/day in children.[18] Due to the lack of consensus in this area, OIAC recommendations do not set a specific threshold, but instead note the variation across different guidance documents.

OIAC recommendations also differentiate between the management of individuals receiving low-dose glucocorticoid therapy versus those who may be on lower doses due to tapering strategies. Due to the immunosuppressive effects of long-term high-dose therapy prior to tapering,[50] these individuals were categorized under Group B and require risk-benefit assessment to inform appropriate PEP strategies. Susceptible individuals on low-dose corticosteroid therapies are classified under Group C and may safely receive MMR as PEP.[16,17]

Azathioprine

While it is generally accepted that azathioprine doses ≤3 mg/kg/day result in low-level immunosuppression, consulted experts indicated that myelosuppression may still be observed at these doses. Indeed, studies and reports have noted bone marrow suppression resulting from azathioprine therapy with doses ≤3 mg/kg/day in children and adults,[51–54] particularly in those with thiopurine S-methyltransferase gene (*TPMT*) polymorphisms.[55–57] To address these concerns, a footnote has been included in the OIAC recommendations (Table 1, footnote L) that encourages vigilance for signs of myelosuppression and adoption of PEP strategies according to the individual's immune status.

Therapies That Target Immune System Components

There have been an increasing number of therapies that specifically target immune system components (e.g., monoclonal antibodies [mAb], small molecule inhibitors) in recent decades. Vaccination guidance often groups these targeted therapies together without distinction between the different classes, targets or impact on the immune system, with novel therapies often being overlooked. OIAC recommendations aim to provide more detailed guidance that encompass many commonly used classes of targeted therapies.

- **Rituximab and other B cell depleting agents**: In general, B cell depleting therapies (e.g., rituximab) have been shown to strongly impair the immune response, with immune reconstitution starting approximately 6 months post treatment with additional time to return to normal. [58–61] OIAC recommendations classify B cell depleting agents within 12 months in Group A, aligned with other PEP guidance documents that list this drug class as highly immunosuppressive.[13,21] As the rate of immune reconstitution following treatment discontinuation varies between individuals, consultation with the treating specialist may be required to determine immune status and appropriate measles post-exposure management.

- **Alemtuzumab**: Alemtuzumab is a mAb targeting CD52, which is present on T cells, B cells and several other immune cell types.[62] This mAb was included in the OIAC guidance (Group A) due to its potent immunosuppressive effect caused by the depletion of both T and B cells following treatment. Clinical studies have shown that while complete B cell recovery usually occurs within 6 months after treatment discontinuation, recovery of T cell subsets tended to occur more slowly.[63] In individuals receiving alemtuzumab as initial therapy, the median time to recovery of CD4 T cells to ≥200 cells/µL was approximately 6 months post treatment; however, full recovery of CD4 and CD8 T cell subsets may take more than 12 months in individuals who have been previously treated with alemtuzumab.[62,63] These findings served as the basis for the timeframe provided in the recommendation. As the rate of recovery of T and B cell compartments vary following alemtuzumab treatment, consultation with the treating specialist may be required to determine appropriate measles post-exposure management.

- **Anti-thymocyte globulin**: Anti-thymocyte globulin is used to prevent and treat acute kidney transplant rejection and works through T cell depletion and suppression.[64] Due to the severe immunosuppression and increased vulnerability to infections caused by treatment, individuals receiving anti-thymocyte globulin were included in Group A.[64–66]

- **Cytokine inhibitors and co-stimulation blockers**: While immunosuppression caused by cytokine inhibitors (e.g., tumor necrosis factor [TNF] inhibitors, anti-interleukin [IL] 17) and costimulation blockers (e.g., abatacept) are not as profound as those observed by lymphocyte depleting agents, these therapies still negatively impact immune pathways as evidenced by reports of dampened response to infections and vaccines and increased risk of opportunistic infections.[60,61,67–72] As such, susceptibility and risk-benefit assessment are recommended to determine appropriate measles post-exposure management of individuals on these therapies.

- **Therapies that are unlikely to significantly diminish response to vaccines**: Some therapies target specific pathways and do not cause significant immunosuppression or systemic immune deficiencies. For example, IgE blockers (e.g., omalizumab) inhibit pathways specifically involved in allergic/eosinophilic inflammation and are unlikely to suppress the immune response to vaccines or infection.[73–76] While published data are limited, consulted clinical experts indicated that susceptible individuals on such therapies (e.g., IgE blockers, IL-5/IL-4 or IL-13 inhibitors for asthma and allergy) would be able to safely receive the MMR vaccine as measles PEP.

HIV Infection

While CD4 T cell count <200 cells/mm^3 is typically used to define immunodeficiency caused by HIV, low CD4:CD8 ratio is increasingly being recognized as another marker of immune dysfunction in individuals with HIV. Despite the high rates of virological suppression with anti-retroviral therapy (ART), a percentage of patients do not achieve complete immune restoration that is marked by the persistence of a decreased CD4:CD8 ratio despite CD4 T cell count recovery.[77,78] A low CD4:CD8 ratio is associated with increased immune activation, inflammation and immunosenescence as well as an increased risk of serious morbidities and mortality.[79–83] Additionally, it is postulated to be an indicator of HIV persistence or presence of larger HIV reservoirs.[79,84,85] Due to its correlation with immune dysfunction and adverse outcomes, experts consulted recommended the inclusion of CD4:CD8 ratio <0.5 as a criterion for immunosuppression among individuals with HIV in the OIAC measles PEP guidelines.

Chimeric Antigen Receptor (CAR) T-cell Therapy

The increasing use of CAR T-cell therapy to treat hematologic malignancies requires its inclusion in guidance. OIAC categorized it within the highest risk group (Group A) because of the severe immunosuppression caused by the procedure (e.g., cytopenias). CAR T-cell therapy also results in persistent B cell and IgG depletion in up to 38% and 74% of patients, respectively, that may last several years after the procedure.[86] Due to the variation in rates and degree of immune reconstitution among this population, OIAC recommends consultation with specialists when determining the appropriate measles PEP strategy for individuals who have undergone CAR T-cell therapy.

Hematopoietic Stem Cell Transplant (HSCT)

OIAC recommendations acknowledge that the rate of immune reconstitution following HSCT varies between individuals and is impacted by several factors including age, graft source, cell dose, donor-recipient matching, conditioning regimen and other post-transplant interventions (e.g., immunosuppressive therapy).[87,88] To best inform measles post-exposure management, consultation with the treating specialist is recommended.

OIAC recommendations are aligned with current CIG guidance stating that live vaccines are not recommended for individuals <24 months post HSCT.[16] However, OIAC recommendations differentiate between allogeneic (allo-HSCT) versus autologous HSCT (auto-HSCT) to reflect the varying degree of immunosuppression resulting from the two procedures. Due to the toxicity of conditioning regimens used, need for immunosuppressive therapy to prevent graft-versus-host disease or graft rejection, and slower rate of immune reconstitution following allo-HSCT versus auto-HSCT, individuals receiving allo-HSCT remain immunocompromised for a longer period of time than those receiving auto-HSCT.[89–91] As such, OIAC recommendations classify allo-HSCT recipients to Group A up to 24 months post transplant and classify auto-HSCT recipients as Group A if within one year post-transplant and Group B on or after one year post transplant. Individuals with chronic graft-versus-host disease are classified in Group A regardless of time post transplant.

Vaccination of Populations with Immunocompromising Conditions

Several groups have or are currently examining whether certain populations who are immunocompromised may be safely considered for live-attenuated vaccines. For example, a panel of experts in infectious diseases, transplantation, vaccinology and immunology from Canada, United States and Europe determined that MMR and varicella vaccines (but not combined MMRV vaccine) are safe for pediatric liver or kidney transplant recipients and recommended their use in individuals who are >1 year post liver or kidney transplant and 2 months after the last acute rejection episode, meet specific criteria of low-level immune suppression, are clinically well, and can be closely monitored.[92]

Based on the growing literature on this area, OIAC guidance indicates that MMR vaccine may be considered as PEP for certain individuals who are immunocompromised belonging to Group B in consultation with an immunologist or infectious disease specialist. In such cases, it is imperative to use clinical judgement to weigh the risks and benefits of measles PEP and consider the clinical needs and preferences of patients on an individual basis.

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About the Ontario Immunization Advisory Committee

The Ontario Immunization Advisory Committee (OIAC) was established in August 2021 at the request of the Chief Medical Officer of Health. The Committee provides scientific and technical advice to Public Health Ontario on vaccines and immunization matters, including program implementation in Ontario, priority populations, clinical guidance, and vaccine safety and effectiveness.

OIAC's work focuses on publicly funded vaccines and immunization programs in Ontario, and those under consideration for new programming. The OIAC provides advice by applying scientific knowledge and the best available evidence, in addition to feasibility, acceptability and other implementation considerations.

For more information about the OIAC and its members contact secretariat@oahpp.ca.

About Public Health Ontario

Public Health Ontario is an agency of the Government of Ontario dedicated to protecting and promoting the health of all Ontarians and reducing inequities in health. Public Health Ontario links public health practitioners, front-line health workers and researchers to the best scientific intelligence and knowledge from around the world. For more information about PHO, visit publichealthontario.ca.

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